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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Jon A. Wolff, James E. Hagstrom, Sean D. Monahan, Paul M. Slattum, David B. Rozema and Vladimir G. Budker**

Serial No.: **09/881,326**

Filed: **06/14/2001**

Group Art Unit: **1636**

Examiner: **William Sandals**

For: **Intravascular Delivery of Non-Viral Nucleic Acid**

SUPPLEMENTAL INFORMATION

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants have attached information that they believe is pertinent to the examination of this case. In particular, the information has been copied from the file history of the U.S. Patent No. 5,698,531 issued to Nabel *et al.* which is the primary prior art cited in Applicants' case.

Applicants wish to supplement their argument that the '531 patent does not teach transfection of extravascular parenchymal cells. The information provided also supplements the telephone interview held on Thursday, January 16, 2003 between Applicants and the Examiner where Applicants call attention to an article reviewing the state of gene delivery published by Elizabeth Nabel (Circulation. 1995;91:541-548.). Elizabeth Nabel states on page 544, 1st column, last paragraph:

> "Several observations concerning the delivery of recombinant genes and patterns of gene expression can be drawn from these studies. Infusion of vector into normal arteries with an intact endothelium results in transfection of intimal cells (primarily endothelial cells). [at this point, Ms. Nabel cites her own work among others published well after the filing date of the '531 patent.] Injury to the vessel and/or application of pressure to the vector infusate results in delivery of DNA transmurally and gene expression in the media".

This paragraph dictates the overall extent of transfection into blood vessels in 1995 as well as the '531 inventors' ability to 'teach' the art in years prior to 1995: 1) transfection

into intimal cells (1st layer of vasculature without injury; and 2) transfection into medial cells (2nd layer of vasculature) with injury.

As further evidence of the '531 inventors' lack of ability to teach Applicants' delivery methods, Applicants call the Examiner's attention to the file history of the '531 patent. In the amendment filed on November 22, 1993, page 3, the inventors limit their teachings to "site-specifically transforming cells." On page 5 site-specificity is limited to "using physical methods to place the DNA or RNA sequences at specific locations." On page 10 of the '531 amendment, the inventors provide data to show delivery to vessel cells and lack of delivery to extravascular cells by β-galactosidase activity: "In addition, no β-galactosidase activity was observed in random microscopic segments from the liver, lung, or kidney, except for cells with endogenous activity."

Importantly, on page 19 of the same amendment, the '531 inventors attempt to differentiate their process from a prior art process and thereby limit their '531 teachings to a physical method of delivery (injury to the endothelial wall): "Firstly, Myers [prior art to Nabel *et al.*] differs from the present invention in that it uses the vector as a homing beacon to ensure that the DNA sequence reaches the appropriate cell. In contrast, the present invention uses physical methods to deliver recombinant genes to specific lesions *in vivo* and differs from Myers targetable injectable vector." Applicants point out that in the '531 inventors' own language they state that they must deliver to "specific lesions" which are caused by their denuding processes and differs from an injectable vector.

In a further limitation to the '531 teachings, Paper 19, an Office Action to the '531 inventors, states on page 2: "Clearly a syringe, as would be used for injection purposes, would be materially distinct from the balloon catheter". In Paper 26, an examiner interview summary record attempts to convince Nabel *et al.* to "reduce issues of prior art" by limiting their claims to a balloon catheter, stating: "Examiner suggested bringing out balloon catheter concept in the method claims." Nabel *et al.* respond and finally limit their claims to a catheter.

By their own statements, the inventors of the '531 patent have limited their teachings to physical denuding of vessel walls followed by physical delivery to specific locations of a vessel wall. One would have to ignore logic to conclude that the '531 patent teaches non-local delivery of genetic material to extravascular parenchymal cells by injection as taught by Applicants.

Applicants request that the Examiner contact them regarding this correspondence after his consideration.

Respectfully submitted,

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I hereby certify that this correspondence is being sent by facsimile transmission to art unit 1636, 703.308.4242: Commissioner for Patents, Washington, DC on Thursday, January 16, 2003.

Signature

44. The method according to Claim 42, wherein said disease is restenosis.

45. The method according to Claim 42, wherein said disease is atherosclerosis.

46. The method according to Claim 42, wherein said DNA or RNA sequence encodes an angiogenic factor.

47. The method according to Claim 36, wherein said sequence is a DNA sequence.

48. The method according to Claim 36, wherein said sequence is a RNA sequence.

49. The method according to Claim 47, wherein said DNA is antisense DNA.--

REMARKS

Claims 22-49 are pending in this application. Reconsideration is respectfully requested.

Applicants wish to thank Examiner Stone for the opportunity to discuss this application at length on September 23, 1993. The substance of that discussion has been incorporated into the following remarks. The experimental results presented during the slide presentation, including both the animal and human studies, have been incorporated into the attached declarations.

The present invention relates to the treatment of diseases by site-specifically transforming cells *in vivo*. *In vivo* gene therapy has several advantages over conventional *ex vivo* gene therapy techniques for the treatment of human disease. *Ex vivo* gene therapy requires the removal of tissues

analogs thereof, interferon α, β or gamma, adhesion molecules, thymidine kinase, diphtheria toxin, pertussis toxin, bacterial or viral superantigens, or drug-sensitive proteins are also useful.

Site-specific instillation of these various genes is achieved using physical methods to place the DNA or RNA sequences at specific locations. Preferred methods include directly injecting the DNA or RNA sequences into a tissue or into the circulation which profuse an involved tissue or, alternatively, introducing the DNA or RNA sequences *via* a balloon catheter which isolates these sequences into a specific region of the arterial wall near the involved tissue. By transforming the cells in a blood artery, expressed therapeutic gene products are steadily profused downstream into the involved tissue. Alternatively, the DNA or RNA sequences can be introduced *in vivo* surgically or percutaneously. The DNA or RNA sequences can be administered *per se* or *via* a vehicle such as a viral vector, a liposomal complex, a cell line or as a complex with a chemical carrier.

The invention relies on recombinant gene expression within transduced vascular cells in a localized arterial segment of a patient to transmit a therapeutic agent encoded by the instilled DNA or RNA sequence to the involved tissue. The methodology of the present inventions has been successfully demonstrated to provide functional expression of various gene products. In addition, the present invention is the first methodology approved by the Recombinant DNA Advisory Committee of the National Institute of Health for direct

not detected in the serum after the initial retroviral infection or during analysis of arterial segments up to 5 months after infection (Table 1). In addition, no ß-galactosidase activity was observed in random microscopic segments from the liver, lung, or kidney, except for cells with endogenous activity (Table 1).

Declaration II demonstrates that the gene transfer method of the present invention does not induce either as to autoimmunity or diffuse toxicity in animals; nor does it result in an uptake of DNA into gonadal tissue. In these experiments, mice, rabbits and pigs were transduced with liposomes containing a recombinant human gene in a eukaryotic plasmid expression vector. The plasmid expression vector encoded either a E.coli ß-galactosidase gene, a human factor IX gene, a human platelet-derived growth factor B gene, a human acidic fibroblast growth factor gene, a human transforming growth factor-ß gene, a human transforming growth factor α gene, the human class I major histocompatibility complex (MHC) gene or a murine class I MHC gene.

Expression of the recombinant genes encoding MHC genes were analyzed in animals to 126 days following direct gene transfer. DNA was prepared from transfected and non-transfected arteries, ovary, testes, heart, lung, liver, spleen, kidney and skeletal muscle. No long-term toxicity in pigs occurred following expression of a human foreign histocompatibility gene. Further, no evidence of either immunity or toxicity was observed in mice injected with the murine class I MHC gene (see Table 1).

35 U.S.C. §102(b)

The rejection of Claims 17, 21, 23, 26, 27, and 32-34 under the above statute as being anticipated by Myers is respectfully traversed. Myers describes coupling an DNA or RNA sequence to a targeting vector vehicle and subsequently internalizing the same into a cell. Firstly, Myers differs from the present invention in that it uses the vector as a homing beacon to ensure that the DNA sequence reaches the appropriate cell. In contrast, the present invention uses physical methods to deliver recombinant genes to specific lesions *in vivo* and differs from Myers targetable injectable vector. Secondly, Myers method is limited to *ex vivo* transformation of cells followed by *in vivo* implantation. Accordingly, Myers et al does not disclose the site-specific transformation of cells with a DNA or RNA sequence. In fact, the method which is described by Myers, i.e., a targetable injectable vector, has yet to be proven successful and is not readily practiced by those skilled in the art.

35 U.S.C. §102(e)

The rejection of Claims 17, 21, 22, 26 and 30 under the above statute as being anticipated by Smith is respectfully traversed. Smith describes a method of using antisense ligand nucleotides to deplete or substantially deplete bone marrow of malignant cells prior to autologous bone marrow transplantation. The selected antisense oligonucleotides have a sequence that is complementary or substantially complementary to a sequence of RNA transcribed from a gene

Claims 21-35 are accorded a filing date of June 28, 1991.

Applicant's election with traverse of Group III in Paper No. 18 is acknowledged. The traversal is on the ground(s) that there has been no showing that the other methods of transformation would work, nor that they would be materially different from the apparatus of group I. Applicant further argues that restriction between groups II and III is improper as the groups do not fall into any of the categories set forth in M.P.E.P. 806.05(e-i). This is not found persuasive because, as to the restriction between groups I and II, the examiner set forth reasonable examples of methods for which the apparatus of group I would not be required. Clearly a syringe, as would be used for injection purposes, would be materially distinct from the balloon catheter apparatus of group I. As to whether injection would be efficacious, applicant admits that "the altered cells or appropriate vector may be surgically, percutaneously or intravenously introduced", and page 5 of the amendment filed June 28, 1991, states that "any of the administrations may be performed by IV or IM injection or subcutaneous injection using any known means, or by the use of the catheter in accordance with the present invention." Thus it does not appear that applicant recognizes the balloon catheter apparatus of group I to be necessary to practice the invention. Moreover, column 1, paragraph 2 of the Myers patent discloses conventional transfection techniques, none of which require the use of a

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/724,509	6/28/91	Nabel	

EXAMINER	
Stone	
ART UNIT	PAPER NUMBER
1804	26

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Mr. Goolkasian (3) Karen Shannon

(2) Exr. Stone (4)

Date of interview 6/20/94

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description:

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed: all in general

Identification of prior art discussed: all in general; Myers, Wang

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicants will consider re-filing the case with a set of claims ranging in scope. Examiner indicated that reduction of scope would likely reduce issues of prior art. Examiner suggested bringing out balloon catheter concept in the method claims.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

Stone
Examiner's Signature

PTOL-413 (REV. 1-84)

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